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Synopsis of the original article ***'Oral Semaglutide and Cardiovascular Outcomes in High-Risk Type 2 Diabetes'***

McGuire DK, et al. N Engl J Med. 2025;
DOI: 10.1056/NEJMoa2501006

Synopsis created and reviewed by Novo Nordisk

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Background

Oral semaglutide



glucagon-like peptide-1 receptor agonist

Proven cardiovascular safety in people with type 2 diabetes at high cardiovascular risk[1]

The SOUL trial assessed cardiovascular effects in people with type 2 diabetes and atherosclerotic cardiovascular disease and/or chronic kidney disease[2]

1. Husain et al. N Engl J Med 2019;381:841–851; 2. McGuire DK, et al. N Engl J Med. 2025;10.1056/NEJMoa2501006

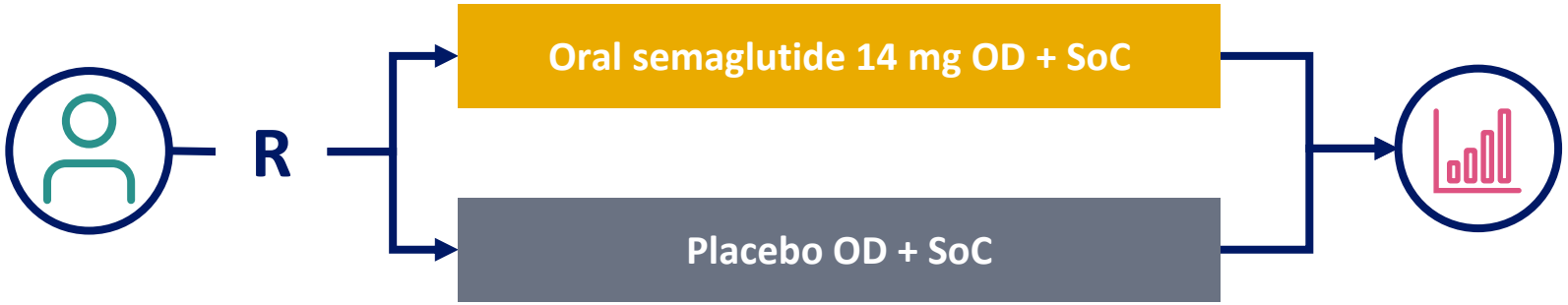
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Methods

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SOUL was a double-blind, placebo-controlled, event-driven, superiority trial



Eligibility criteria

- ≥50 years of age
- Glycated hemoglobin level 6.5–10.0%
- Known atherosclerotic cardiovascular and/or chronic kidney disease

Primary outcome

- Time to first major adverse cardiovascular event:
  - death from cardiovascular cause
  - nonfatal myocardial infarction
  - nonfatal stroke

OD, once daily; R, randomization; SoC, standards of care

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Results

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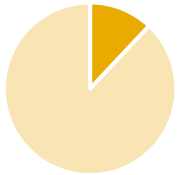
9650
participants randomized

Mean (±SD) follow-up was **47.5±10.9 months** (median 49.5 months)

Concomitant use of **SGLT2is** at baseline was **26.9%** in each group

Primary outcome

The incidence of MACE was significantly lower in the oral semaglutide group (rate 3.1 per 100 person-years) compared with placebo (rate 3.7 per 100 person-years); **HR, 0.86; 95% CI, 0.77–0.96; P=0.006**



12.0%
579/4825 participants receiving oral semaglutide

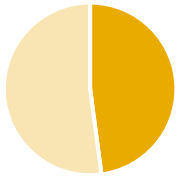
VS



13.8%
668/4825 participants receiving placebo

Adverse events

Serious adverse events were less common with oral semaglutide than with placebo, **P=0.02**



47.9%
in the oral semaglutide group

VS



50.3%
in the placebo group

There was a higher incidence of gastrointestinal disorders with semaglutide (5.0% vs 4.4%)

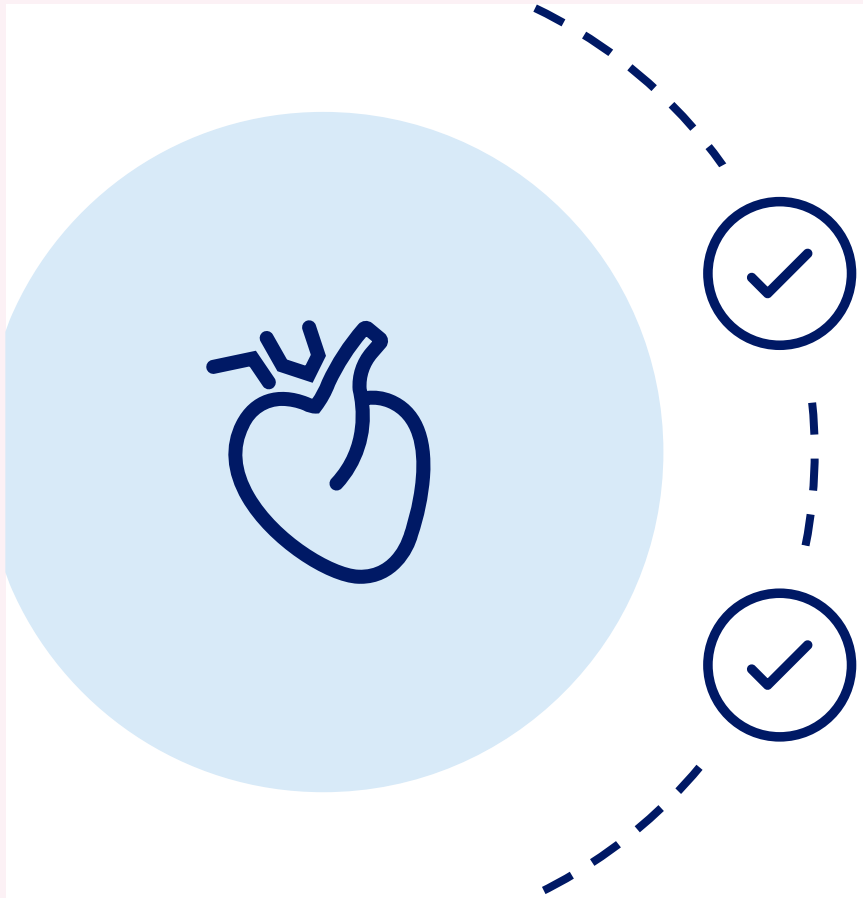
CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiovascular event; SD, standard deviation; SGLT2i, sodium-glucose co-transporter-2 inhibitor

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Conclusion



Oral semaglutide significantly reduced major cardiovascular events in people with type 2 diabetes and atherosclerotic cardiovascular disease and/or chronic kidney disease[1]

The overall **safety profile** of oral semaglutide in SOUL was **consistent** with that seen in previous trials with semaglutide,[2] and **no new safety signals** were observed[1]

1. McGuire DK, et al. N Engl J Med. 2025;10.1056/NEJMoa2501006; 2. Aroda et al. Diabetes Obes Metab 2023;25:1385–1397

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